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STEPHEN DONOVAN
LEGAL DEPTALLERGAN INC TOWER TWO 7TH FLR
2525 DUPONT DRIVE
IRVINE, CA 926239534

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 24

Application Number: 09/371,354
Filing Date: August 10, 1999
Appellant(s): DONOVAN, STEPHEN

Frank J. Uxa
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 06 October 2003 (hereinafter, the Brief).

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 7, 15-17, and 37-38 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Tsuboi, Masato et al. "Botulinum neurotoxin A blocks cholinergic ganglionic neurotransmission in the dog heart" Jpn J Pharmacol 89(3): 249-254, 2002.

Mangrum et al. "The evaluation and management of bradycardia" N Eng J Med 342(10): 703-709, 2000.

Tsuboi M et al. "Inotropic, chronotropic, and dromotropic effects mediated via parasympathetic ganglia in the dog heart" Am J Physiol Heart Circ Physiol 279: H1201-H1207, 2000.

Johnson, E. "Clostridial toxins as therapeutic agents: benefits of nature's most toxic proteins" Annu Rev Microbiol 53: 551-575, 1999.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 7, 15-17, and 37-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The basis for this rejection is set forth in the previous Office Actions (Paper No. 6, 05 July 2001; Paper No. 11, 25 February 2002; Paper No. 18, 18 October 2002; Paper No. 21, 01 July 2003).

Claims 7, 15-17, and 37-38 are directed to a method for treating bradycardia comprising intrapericardial injection of a botulinum toxin to the sinoatrial (SA) node or to the atriovenctricular (AV) node of a heart of a patient with bradycardia to treat bradycardia. Claim 15 recites that botulinum toxin is botulinum toxin A and is locally administered to the heart in an amount between 0.01 U/kg and 35 U/kg. Claim 16 recites that botulinum toxin is botulinum toxin A and is locally administered to the heart in an amount between 0.1 U/kg and 30 U/kg.

Claim 17 recites that botulinum toxin is botulinum toxin A and is locally administered to the heart in an amount between 1U/kg and 25 U/kg. Claim 37 recites that the botulinum toxin is selected from the group consisting of botulinum toxin types A, B, C, D, E, F, and G.

The specification teaches a prophetic procedure for treating bradycardia by intrapericardial injection of a botulinum toxin. The specification teaches that "intrapericardial injection of BOTOX to treat an arrhythmia such as bradycardia is carried out by inserting a needle tip of a syringe through the unopened chest wall, and guided by fluoroscopy, through the thin fibrous baglike structure of the pericardium which surrounds the heart and into a pericardial sinus" (pg 31, lines 6-10). The specification continues to disclose that a bolus injection of the botulinum toxin can be released into a sinus, such as the transverse pericardial sinus adjacent to either the SA node or the AV node (pg 31, lines 11-13). The specification teaches that the toxin may be released at a location within the pericardium, under the endocardium, intermediate between the SA and AV nodes so as to maximum toxin contact with vagal nerve termini (pg 31, lines 15-17). Alternative intrapericardial procedures access the normal pericardial space through the right atrial appendage or by subxyphoid access (pg 31-32). The specification also discloses that between about 10 U and 300 U of BOTOX are administered and that the unit amount depends on the age and health of the patient, size of the patient's heart, and the mass of arrhythmic cardiac tissue of the patient's heart (pg 33, lines 4-14).

However, the specification does not disclose any methods or working examples that administer a botulinum toxin to a cardiac muscle or cells *in vitro* or *in vivo,* particularly by intrapericardial injection to achieve and effect on cardiac tissue rhythm. The specification also does not teach any specific subjects that have a cardiac muscle disorder and that are treated

successfully by any procedure with a botulinum toxin. The specification does not teach the time period in which the toxin should be administered or for how long (for example, before, during, or after surgery) and any side effects that are experienced after the administration of the botulinum toxin. The specification does not disclose a *specific* dosage of botulinum toxin that should be administered to a subject, but teaches that "botulinum toxin passes unattenuated through the lining of the gut and attacks the central nervous system...symptoms of botulinum intoxications progress from difficulty walking, swallowing, and speaking to paralysis of the respiratory muscles, resulting in suffocation and death" (pg 12, lines 12-16). There is no guidance in the specification as to the safe dosage and duration of administration of any botulinum toxin to the cardiac muscle. Although the specification discloses ranges of botulinum toxin that could be administered to a patient, depending on weight, size, age, disease severity and responsiveness to therapy (pg 24-26), undue experimentation would be required of the skilled artisan to determine the optimal dose of botulinum toxin to be administered without damage to the heart for every patient. The determination of such is not trivial considering the wverity fo the effects of botulinum toxin in the body. The relevant literature reports that botulinum toxin A has only been effective in the treatment of involuntary muscle contraction disorders, dystonias, and spasticity in focal or segmental muscle regions (pg 565; Johnson, E. Annu Rev Microbiol 53: 551-575, 1999). Additionally, the primary complications of botulinum toxin therapy have been "(a) formation of antibodies and obliteration of response to type-A toxin, (b) lack of alternate botulinum serotypes with the potency and duration of action of type A, (c) diffusion of botulinum toxin to neighboring muscles with transient and sometimes debilitating aptosis, (d) lack of consistency and low specific activities of certain toxin preparations, and (e) the need for

repeated injection of toxin in chronic disorders" (pg 566, pp 1). Neither the specification nor the prior art have overcome these obstacles. The present invention is unpredictable and complex wherein one skilled in the art may not necessarily treat bradycardia by intrapericardial injection of a botulinum toxin to a cardiac muscle. Although the claimed method utilizes routine intrapericardial injection techniques, the results of the method are unpredictable and complex when combined with the step of administering any botulinum toxin.

Due to the large quantity of experimentation necessary to treat bradycardia by administering any botulinum toxin to the SA node or AV node of the heart and to determine the dosage and safety of botulinum toxin and the timing and duration of administration without irreversible injury or actually killing the patient, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the contradictory state of the prior art (see Johnson, E.), and the unpredictability of the effects of any botulinum toxin on a subject, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

(11) Response to Argument

Appellant argues at page 4 of the Brief that the Patent Office has essentially discounted the factual evidence presented in three declarations provided by two experts in the field, i.e. two declarations by Dr. Longhurst (expert in the field of cardiovascular medicine) and one declaration by Dr. Brin (expert in the field of botulinum toxin therapy). Appellant asserts that based upon independent review, each expert has concluded that the instant application contains sufficient disclosure of a method of treating bradycardia using a botulinum toxin to enable one of

ordinary skill in the art to practice the invention without undue experimentation. Specifically, at the bottom of page 4 through page 5 of the Brief, Appellant quotes sections of the Longhurst declarations (Longhurst #1 (12/5/2001, Paper No. 9) and #2 (4/29/2002, Paper No. 13)) to establish that the specific time period in which the toxin should be administered or for how long and the specific dosage of the botulinum toxin entail considerations of the patient's size, weight, age, and disease severity, which are routine considerations determined on a patient by patient basis by a cardiologist who has knowledge of the therapeutic use of a botulinum toxin. Appellant also quotes from the Longhurst declaration #2 to emphasize that for a patient with sympathetic bradycardia, vagal nerve inhibition and an increase in heart rate can be accomplished by administration of botulinum toxin into an existing pericardial space to increase the heart rate of a patient with symptomatic bradycardia. However, the Longhurst declarations under 37 CFR 1.132 filed 05 December 2001 (Paper No. 9) and 29 April 2002 (Paper No. 13) are insufficient to overcome the rejection of claims 7, 15-17, and 37-38 based upon lack of enablement under 35 U.S.C. §112, first paragraph. The Longhurst declaration #1 is not found to be persuasive because the declarant (Dr. Longhurst) states his position without any scientific reasoning or evidence as to why one skilled in the art would successfully be able to treat bradycardia by administering a botulinum toxin to the pericardial space of a human patient. The Longhurst declaration #2 is not found to be persuasive because although Dr. Longhurst has extensive training and experience as a scientist and physician in cardiovascular medicine, Dr. Longhurst has not worked with any botulinum toxins. Additionally, Dr. Longhurst has not investigated what effects local administration of botulinum toxin has upon any internal body organ, particularly the heart. Although the second paragraph of the declaration may be well

known scientific facts about the heart (see also page 5, ¶ 2 of the Brief), the skilled artisan cannot predict that intrapericardial injection of any botulinum toxin into the SA or AV node of the heart of patient will produce the desired response, i.e. an increased heart rate, because the heart is a complex organ and numerous challenges of botulinum therapy have been reported (Johnson, E. Ann Rev Microbiol 53: 551-575, 1999; pg 566). Therefore, the submitted declarations are an allegation and are insufficient to overcome the rejection of the claims under 35 U.S.C. § 112, first paragraph, enablement.

Additionally, Appellant indicates at page 6 of the Brief that the declaration of Dr. Brin (20 February 2003, Paper No. 20) establishes that Dr. Brin is a well-established expert in the field of botulinum toxin therapy. Appellant contends that according to the declarant's opinion, a patient with bradycardia, vagal nerve inhibition and hence an increase in heart rate can be accomplished by intrapericardial injection of a botulinum toxin to the SA node or to the AV node of the heart without undue experimentation. Appellant indicates the Brin declaration states that matters such as the specific time period in which the toxin should be administered or for how long, and the specific dosage of the botulinum toxin to use entail consideration of factors such as the patient's size, weight, age, and disease severity which factors are routine considerations determined on a patient by patient basis by the treating physician who has knowledge of the therapeutic use of a botulinum toxin. The Brin declaration also relies upon a post-filing date reference (Masato et al. Jpn J Pharmacol 89(3): 249-254, 2002) to corroborate the operability of the claimed invention and mitigate against the alleged contradictory nature of the prior art alleged by the Examiner (pg 7, ¶ 3 of the Brief). The Brin declaration relies upon Masato et al. as purported evidence to indicate that the administration of a botulinum toxin to the SA node of a

dog heart blocks parasympathetic mediated bradycardia. It is noted that Appellant refers to this reference as Masato et al. although the author's first name is Masato and the author's last name is Tsuboi. The Examiner referred to this reference in previous Office Actions as Tsuboi et al. (2002). However, for uniformity, the Examiner will also refer to this citation as Masato et al.

The Brin declaration under 37 CFR 1.132 filed 20 February 2003 (Paper No. 20) is insufficient to overcome the rejection of claims 7, 15-17, and 37-38 based upon lack of enablement under 35 U.S.C. § 112, first paragraph. Although Dr. Brin has a distinguished career and was one of the first investigators to examine the use of botulinum toxin for treatment of medical disorders, the declaration filed in the instant case is based upon opinion. The contradictory factual evidence in the Masato et al. reference outweighs the opinion of the declarant. For example, as discussed in further detail below, Masato et al. teaches a canine model system that is not predictive of the scope of the claims for several reasons. Masato et al. utilize *electrically stimulated* preganglionic parasympathetic nerves of the canine heart to induce bradycardia, which may be physiologically different from bradycardia normally induced by various intrinsic, extrinsic, or damaging factors that normally induce bradycardia. Masato et al. also do not teach treatment of bradycardia by administration of any botulinum toxin to the AV node, which is required by the claims. Therefore, whatever evidence is presented in Masato et al. is not commensurate in scope with the claims. Masato et al. specifically inject botulinum toxin A into the *SA fat pad*, rather than any non-specific botulinum toxin into the *SA node or AV node*. Masato et al. utilize much smaller amounts of botulinum toxin A than the high range dosages recited in the claims. It is also noted by the Examiner that Dr. Brin is currently

employed by Allergan, the assignee of the instant application, and therefore is a party of interest in the outcome of the case.

At page 8 of the Brief, Appellant submits that the Masato et al. reference demonstrates that the administration of a botulinum toxin to a region of the heart containing parasympathetic neurons blocks bradycardia mediated by parasympathetic neuronal activity. Appellant argues at pg 8 of the Brief (2nd full paragraph) that the Masato et al. reference and Brin declaration establish that botulinum toxin is administered to a single region of the heart with a substantial number of parasympathetic neuronal processes, and that after injecting the botulinum toxin into the region, the symptoms of bradycardia are treated. Although Masato et al. may have injected botulinum toxin A into a canine heart, the canine model system of Masato et al. is not predictive of the scope of the instant claims. For instance, Masato et al. disclose that a decrease in heart rate is induced by stimulation of the preganglionic parasympathetic nerves in the heart by *electrical stimulation* (abstract; pg 250, ¶ 4). However, the state of the art teaches that bradycardia in patients is caused by either intrinsic dysfunction of or damage to the conduction system or by the response of normal tissues to extrinsic factors (Mangrum et al. N Eng J Med 342(10): 703-709, 2000; see pg 703, ¶ 1; pg 704, col 2 through pg 705; Table 1). There is no guidance in the specification or prior art indicating that electrical stimulation of the preganglionic parasympathetic nerves of the heart is a model system for bradycardia. There are also many details in Masato et al. regarding the electrical stimulation methodology which are not disclosed in the instant specification or prior art (see Masato et al., pg 250, ¶ 4). Therefore, Masato et al.'s treatment of *electrically stimulated* preganglionic parasympathetic nerves of the canine heart with botulinum toxin A is not predictive of treating bradycardia in general with

botulinum, wherein the bradycardia may be caused by numerous intrinsic, extrinsic, or damaging factors, such as collagen vascular diseases, surgical trauma, drugs, hypothermia, etc. (Mangrum, Table 1).

Furthermore, the canine experiments of Masato et al. are not commensurate in scope with the instant claims because Masato et al. disclose injecting botulinum A into the sinoatrial (SA) fat pad, while the claims recite intrapericardial injection of a botulinum toxin to the SA node or AV node of the heart. Tsuboi et al. (Am J Physiol Heart Circ Physiol 279: H1201-H1207, 2000; pg H1201, col 1) indicate that parasympathetic ganglionic cells exist in the fatty tissue overlying the right atrial junction of the right pulmonary veins in the heart, called the SA fat pad (pg 249, ¶ 2, col 2). Mangrum et al. state that the sinus node is a collection of specialized cells located in the sulcus terminalis at the junction of the superior vena cava and the right atrium (pg 703, col 2). Therefore, the state of the art is such that the SA node and AV node are specialized clusters of cells in the heart which differ from fatty tissue of the SA fat pad, which contains parasympathetic ganglionic cells. One skilled in the art would not be able to predict that injection of botulinum into the SA node or AV node would treat bradycardia based on the Masato et al. reference because the cited reference and the instant claims inject botulinum toxin into different parts of the heart, which may produce different effects in the subject. It is noted that at pg 8 (first full paragraph) of the Brief, Appellant indicates that in the Brin declaration, Dr. Brin, interprets the disclosure of a sinoatrial fat pad injection similar to a sinoatrial node injection. However, although Dr. Brin is an expert in the use of botulinum toxins for therapeutic use, Dr. Brin is not a cardiologist or an expert about the heart. Dr. Brin's interpretation is an

opinion and his position is stated without any scientific reasoning or evidence as to why a sinoatrial fad pad injection is the same or similar to a sinoatrial injection.

The Masato et al. reference relied upon by Appellant also does not teach injection of any botulinum toxin into the AV node of the heart. Masato et al. specifically indicate that botulinum toxin A is injected into the SA fat pad only (abstract; pg 249, ¶ 2; pg 250, col 2). Therefore, the skilled artisan still must resort to trial and error experimentation to inject all possible types of botulinum toxin into the AV node to treat bradycardia.

Additionally, the canine model system of the Masato et al. reference is not predictive of the scope of the instant claims because Masato et al. teach administering botulinum toxin A, while the claims require the administration of any botulinum toxin. Undue experimentation is required by one skilled in the art to determine the optimal type of botulinum toxin to treat bradycardia. The specification of the instant application even discloses that different serotypes of botulinum toxin (i.e., A, B, C1, D, E, F, G) vary in the animal species that they affect and in the severity and duration of the paralysis they evoke (specification pg 12, lines 28-29; pg 13, line 1). Therefore, the substitution of one botulinum toxin for another in the claimed methods will still require trial and error experimentation to determine each toxin's optimal dosage and duration of administration for every patient without damaging the patient's heart. Masato et al. also teach only administering 20-25 mouse units of botulinum toxin A to dogs who weighed between 15-28 kg (pg 250, ¶ 2; ¶ 5). Accordingly, the dogs in Masato et al. are administered between 0.71 U/kg and 1.7 U/kg of botulinum toxin A (for example, 25units/15 kg and 20 units/28kg). Although these dosages overlap with the dosage ranges recited in claims 15-17, the Masato et al. dosages are low in comparison with the 25 U/kg-35 U/kg dosages that are recited in

the claims. The specification of the instant application does not teach the skilled artisan a specific optimal dosage or duration of treatment of any botulinum toxin to the SA node or AV node of the heart. Undue experimentation would be required of the skilled artisan to determine the optimal dose of botulinum toxin to be administered to every patient without damaging the heart.

Appellant argues at the bottom of page 8 of the Brief and at pg 21 of the Brief that it is well established that working examples are not required in a patent application if the specification contains a sufficient disclosure of the invention so that one skilled in the art can practice the invention without an undue amount of experimentation (*In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)). Appellant also asserts that the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claims (page 11-13 of the Brief). Appellant indicates that examples are provided regarding the use of botulinum toxin type A and that the specification as a whole provides sufficient guidance regarding the use botulinum toxin to treat bradycardia (pg 11, ¶ 3; pg 15-18, 21 of Brief). Appellant contends that the specification discloses how a botulinum toxin is administered to a patient to enable one of ordinary skill in the art to administer a botulinum toxin without undue experimentation (pg 16 of the Brief). Appellant states that the specification discloses dosage ranges for treatment of bradycardia as well as that the administration of a botulinum toxin to cardiac tissue, such as the SA or AV node, alleviates the symptoms of bradycardia (pg 11-12 of the Brief). Appellant states that it is not necessary to specify the specific dosage or duration of administration if it is obvious to one skilled in the art that such information could be obtained without undue experimentation. Appellant cites *U.S. v.*

Telectronics, Inc. 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) (pg 9, first full ¶ of the Brief; pg 19). Appellant submits that parameters such as dosages and timing and methods of administration of therapeutic agents may need to be optimized, but optimization is considered routine to persons of ordinary skill in the art (pg 19 of the Brief). Appellant asserts that substitution of one type of botulinum toxin for another type of botulinum toxin to treat bradycardia would not require undue experimentation since each of the different types of botulinum toxins are known to inhibit acetylcholine release, which is disclosed in the specification (pg 20 of the Brief).

Although Appellant need not actually have reduced the invention to practice prior to filing the application, the lack of a working example is only one factor to be considered, especially in a case involving an unpredictable art (MPEP § 2164.02). The specification at pg 31-33 only outlines a prophetic procedure for treating bradycardia by administering botulinum toxin A to an SA node to an AV node of a heart of a patient. However, this is not adequate guidance, but is merely an invitation for the artisan to use the current invention as a starting point for further experimentation. For example, the prophetic example does not teach the skilled artisan the *optimal* dosage and duration of administration of botulinum toxin A so as to avoid causing irreparable damage or death to the patient from this toxin. The specification only teaches that "the specific unit amount of BOTOX to locally administer depends upon a number of factors,...including the age and health of the patient, the size of the patient's heart, the mass of the arrhythmic cardiac tissue of the patient's heart, the local administration route and mechanism chosen, etc." (pg 33, lines 10-14). Furthermore, the claimed method may not necessarily treat bradycardia. The skilled artisan must resort to trial and error experimentation to determine the optimal dosage and duration of administration of numerous types of botulinum toxins for every

patient without damaging the patient's heart. Such trial and error experimentation is considered undue. Although Appellant submits that parameters such as dosages and timing and methods of administration of therapeutic agents may need to be optimized and that optimization is routine, there is little guidance in the specification for one skilled in the art to determine these optimal conditions. For example, the claims and the specification disclose that the botulinum administered to the heart may be between about 0.01 U/kg and about 35 U/kg. For comparison, Masato et al. teach administering only 20-25 mouse units of botulinum toxin A to dogs who weighed between 15-28 kg (Masato et al., pg 250, ¶ 2, ¶ 5). Accordingly, the dogs in Masato et al. are administered between 0.71 U/kg and 1.7 U/kg of botulinum toxin A (for example, 25units/15 kg and 20 units/28kg). Although these dosages overlap with the dosage ranges recited in claims 15-17, the Masato et al. dosages are low in comparison with the 25 U/kg-35 U/kg dosages that are recited in the claims. The specification of the instant application does not teach the skilled artisan a specific dosage or duration of treatment of any botulinum toxin to the SA node or AV node of the heart. It is noted that the fact pattern of *U.S. v. Telectronics, Inc.* 8 USPQ2d, 1217, 1223 (Fed. Circ. 1988) (cited by the Applicant) and the fact pattern of the instant rejection are significantly different, and the court decision is not binding with regard to the instant rejections. (The issues in *U.S. v. Telectronics, Inc.* revolve around patent infringement, patent validity, and adequacy of disclosure of the specification.) A specification may be enabling even though some experimentation is necessary, but the amount of experimentation, however, must not be unduly extensive. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed". Additionally, as was found in Ex parte

Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present invention is unpredictable and complex wherein one skilled in the art may not necessarily treat bradycardia by intrapericardial injection of a botulinum toxin to an SA node or AV node of a heart of a patient. Although the claimed method utilizes routine intrapericardial injection techniques, the results of the method are unpredictable and complex when combined with the step of administering any botulinum toxin. There is no information in the art regarding injection of botulinum toxins into major organs of the body for therapeutic treatment and the invention of the instant application is not disclosed in the specification in such a manner that one skilled in the art will be able to practice it without undue experimentation. Also, although botulinum toxins may block the release of acetylcholine, the specification discloses that different serotypes of botulinum toxin (i.e., A, B, C1, D, E, F, G) vary in the animal species that they affect and in the severity and duration of the paralysis they evoke (specification pg 12, lines 28-29; pg 13, line 1). Therefore, the substitution of one botulinum toxin for another in the claimed methods will still require trial and error experimentation to determine each toxin's optimal dosage and duration of administration for every patient to treat bradycardia.

Appellant contends that the quantity of experimentation that may be necessary to practice the invention is minimal and is not undue in view of Appellant's disclosure (pg 14, ¶ 1).

Appellant also argues that any such experimentation may be routine as evidenced by the Longhurst declarations (#1 and #2) and the Brin declaration (pg 14, 21 of the Brief). Appellant submits that the specification has incorporated by reference several prior art references to support the fact that such steps are well-known and practiced in the prior art at the time of the invention (pg 14, ¶2 of the Brief). Appellant also indicates that the use of a botulinum toxin as a therapeutic agent is routine for persons of ordinary skill in the art (bottom of pg 14 through pg 15 of the Brief). At page 10, page 21 (¶ 2) and page 23 (¶2) of the Brief, Appellant argues that the claimed invention is not complex or unpredictable because the invention utilizes well-known administration techniques and a therapeutic agent that is known to inhibit acetylcholine release. Appellant states that the administration of botulinum toxin inhibits acetylcholine release to attenuate the reduction in heart rate associated with bradycardia.

As discussed above, the specification at pg 31-33 only outlines a prophetic procedure for treating bradycardia by administering botulinum toxin A to an SA node to an AV node of a heart of a patient. However, this is not adequate guidance, but is merely an invitation for the artisan to use the current invention as a starting point for further experimentation. For example, the prophetic example does not teach the skilled artisan the *optimal* dosage and duration of administration of botulinum toxin A. The claimed method may not necessarily treat bradycardia and the skilled artisan must resort to trial and error experimentation to determine the optimal dosage and duration of administration of numerous types of botulinum toxins for every patient without damaging the patient's heart. Such trial and error experimentation is considered undue. Relevant literature also teaches that the primary complications of botulinum toxin therapy have been "(a) formation of antibodies and obliteration of response to type-A toxin, (b) lack of

alternate botulinum serotypes with the potency and duration of action of type A, (c) diffusion of botulinum toxin to neighboring muscles with transient and sometimes debilitating ptosis, (d) lack of consistency and low specific activities of certain toxin preparations, and (e) the need for repeated injection of toxin in chronic disorders" (pg 566, pp 1). Although Appellant submits that parameters such as dosages and timing and methods of administration of therapeutic agents may need to be optimized and that optimization is routine, there is little guidance in the specification for one skilled in the art to determine these optimal conditions. Appellant indicates that the Longhurst declarations (#1 and #2) and the Brin declaration support the assertion that such experimentation may be routine. However, neither Dr. Longhurst nor Dr. Brin have investigated what effects local administration of botulinum toxin has upon any internal organ, particularly the heart. Both Dr. Longhurst and Dr. Brin indicate that several factors are routine considerations determined on a patient by patient basis by the *treating physician who has knowledge of the therapeutic use of a botulinum toxin* (Longhurst #1, pg 2, point 7; Brin, pg 4, point 16). It is noted that Dr. Longhurst is an expert in the field of cardiovascular medicine but has no training with any botulinum toxins. Although a cardiologist knows how to access the pericardial space of a patient with bradycardia and knows how to inject a pharmaceutical into the pericardial space, this does not mean that a cardiologist or other such skilled artisan can treat bradycardia by injecting a botulinum toxin to an SA or AV nose of a heart of a patient with bradycardia. Dr. Brin is a well-established expert in the field of botulinum therapy, but has no training in cardiovascular medicine. Therefore, neither Dr. Longhurst nor Dr. Brin is a patient's physician that has the knowledge of the therapeutic use of a botulinum toxin. The declarations filed in the instant application are based only upon opinion.

Furthermore, although the claimed method may utilize routine intrapericardial injection techniques, the results of the method are unpredictable and complex when combined with the step of administering any botulinum toxin. Although the prior art recognizes that botulinum toxin inhibits acetylcholine release, the state of the art is also such that botulinum toxin A has only been effective in the treatment of involuntary muscle contraction disorders, dystonias, and spasticity in focal or segmental muscle regions (Johnson, E., pg 565). The specification discloses that botulinum toxin A has become an important pharmaceutical for the treatment of various segmental and peripheral movement disorders associated with muscle overactivity, such as spasticity, as well as pain, and various other neuronal disorders (pg 13, lines 1-6). However, the administration of any botulinum toxin to an *organ,* particularly the heart, to treat a disorder is not routine or well-known in the prior art. Therefore, undue experimentation would still be required by the skilled artisan to determine the optimal dosage and duration of administration of numerous types of botulinum toxins for every patient without damaging the patient's heart as well as to treat bradycardia.

Appellant asserts that the step of administering a therapeutic agent to cardiac tissue is well known in the art and that the prior art has established that acetylcholine release from cholinergic neurons is inhibited by botulinum toxin (pg 21-22 of the Brief). Appellant contends that since the filing date of the instant application, scientists have reported that botulinum toxin locally administered to the cholinergic parasympathetic neurons of the heart successfully alleviates bradycardia-like symptoms associated with cholinergic neuronal activity (Masato et al.; pg 10, 21-22 of the Brief). Appellant adds that this is supported by Dr. Brin's declaration. At pg 22 of the Brief (3rd full paragraph), Appellant argues that Masato et al. conclude that local

administration of botulinum toxin blocks bradycardia mediated by parasympathetic ganglionic activation (abstract, last sentence).

As discussed above, although the claimed method may utilize routine intrapericardial injection techniques, the results of the method are unpredictable and complex when combined with the step of administering any botulinum toxin. Although the prior art recognizes that botulinum toxin inhibits acetylcholine release, the state of the art is also such that botulinum toxin A has only been effective in the treatment of involuntary muscle contraction disorders, dystonias, and spasticity in focal or segmental muscle regions (Johnson, E., pg 565). Although Appellant indicates that scientists (Masato et al.) have reported that botulinum toxin locally administered to the cholinergic parasympathetic neurons of the heart successfully alleviates bradycardia-like symptoms associated with cholinergic neuronal activity, the canine model system of Masato et al. is not predictive of the scope of the instant claims. For instance, Masato et al. disclose that a decrease in heart rate is induced by stimulation of the preganglionic parasympathetic nerves in the heart by *electrical stimulation* (abstract; pg 250, ¶ 4). However, the state of the art teaches that bradycardia in patients is caused by either intrinsic dysfunction of or damage to the conduction system or by the response of normal tissues to extrinsic factors (Mangrum et al. N Eng J Med 342(10): 703-709, 2000; see pg 703, ¶ 1; pg 704, col 2 through pg 705; Table 1). There is no guidance in the specification or prior art indicating that electrical stimulation of the preganglionic parasympathetic nerves of the heart is a model system for bradycardia. There are also many details in Masato et al. regarding the electrical stimulation methodology which are not disclosed in the instant specification or prior art (see Masato et al., pg 250, ¶ 4). Therefore, Masato et al.'s treatment of *electrically stimulated* preganglionic

parasympathetic nerves of the canine heart with botulinum toxin A is not predictive of treating bradycardia in general with botulinum, wherein the bradycardia may be caused by numerous intrinsic, extrinsic, or damaging factors, such as collagen vascular diseases, surgical trauma, drugs, hypothermia, etc. (Mangrum, Table 1).

Furthermore, the canine experiments of Masato et al. are not commensurate in scope with the instant claims because Masato et al. disclose injecting botulinum A into the sinoatrial (SA) fat pad, while the claims recite intrapericardial injection of a botulinum toxin to the SA node or AV node of the heart. (For clarification, Masato et al. state that the results obtained from their experiments indicate that selective injection of botulinum toxin into the SA fat pad (not the SA node, as required by the claims) blocks bradycardia mediated by parasympathetic ganglionic activation in the dog heart (abstract, last sentence)). Tsuboi et al. (Am J Physiol Heart Circ Physiol 279: H1201-H1207, 2000; pg H1201, col 1) indicate that parasympathetic ganglionic cells exist in the fatty tissue overlying the right atrial junction of the right pulmonary veins in the heart, called the SA fat pad (pg 249, ¶ 2, col 2). Mangrum et al. state that the sinus node is a collection of specialized cells located in the sulcus terminalis at the junction of the superior vena cava and the right atrium (pg 703, col 2). Therefore, the state of the art is such that the SA node and AV node are specialized clusters of cells in the heart which differ from fatty tissue of the SA fat pad, which contains parasympathetic ganglionic cells. One skilled in the art would not be able to predict that injection of botulinum into the SA node or AV node would treat bradycardia based upon the Masato et al. reference because the cited reference and the instant claims inject botulinum toxin into different parts of the heart, which may produce different effects in the subject.

The Masato et al. reference relied upon by Appellant also does not teach injection of any botulinum toxin into the AV node of the heart. Masato et al. specifically indicate that botulinum toxin A is injected into the SA fat pad only (abstract; pg 249, ¶ 2; pg 250, col 2). Therefore, the skilled artisan still must resort to trial and error experimentation to inject all possible types of botulinum toxin into the AV node to treat bradycardia.

Additionally, the canine model system of the Masato et al. reference is not predictive of the scope of the instant claims because Masato et al. teach administering botulinum toxin A, while the claims require the administration of any botulinum toxin. Undue experimentation is required by one skilled in the art to determine the optimal type of botulinum toxin to treat bradycardia. The specification of the instant application even discloses that different serotypes of botulinum toxin (i.e., A, B, C1, D, E, F, G) vary in the animal species that they affect and in the severity and duration of the paralysis they evoke (specification pg 12, lines 28-29; pg 13, line 1). Therefore, the substitution of one botulinum toxin for another in the claimed methods will still require trial and error experimentation to determine each toxin's dosage and duration of administration for every patient without damaging the patient's heart. Masato et al. also teach only administering 20-25 mouse units of botulinum toxin A to dogs who weighed between 15-28 kg (pg 250, ¶ 2, ¶ 5). Accordingly, the dogs in Masato et al. are administered between 0.71 U/kg and 1.7 U/kg of botulinum toxin A (for example, 25units/15 kg and 20 units/28kg). Although these dosages overlap with the dosage ranges recited in claims 15-17, the Masato et al. dosages are low in comparison with the 25 U/kg-35 U/kg dosages that are recited in the other claims. The specification of the instant application does not teach the skilled artisan a specific dosage or duration of treatment of any botulinum toxin to the SA node or AV node of the heart. Undue

experimentation would be required of the skilled artisan to determine the dose of botulinum toxin to be administered to every patient without damaging the heart. There are no methods or working examples in the specification to indicate that intrapericardial administration of any botulinum toxin inhibits parasympathetic nerve activity of a bradycardiac heart, resulting in uninhibited sympathetic innervation to increase heart rate.

Finally, Appellant asserts that the instant claims are narrowly tailored to methods for treating bradycardia by intraperitoneally injecting a specific class of neurotoxins, i.e. a botulinum toxin, into specific regions of the heart. Appellant concludes that since the claims are directed to a specific class of neurotoxins that have a common effect on a common population of neurons, and to a specific target site to achieve a therapeutic effect, the claims are not unduly broad (pg 23, last ¶ of the Brief). This argument has been fully considered but is not found to be persuasive. Specifically, claim 7 fails to recite limitations as to the type of botulinum toxin to be injected into the SA or AV node of a heart. Although botulinum toxins inhibit acetylcholine release, the specification discloses that different serotypes of botulinum toxin (i.e., A, B, C1, D, E, F, G) vary in the animal species that they affect and in the severity and duration of the paralysis they evoke (specification pg 12, lines 28-29; pg 13, line 1). Therefore, the substitution of one botulinum toxin for another in the claimed methods would require trial and error experimentation to determine each toxin's dosage and duration of administration for every patient without damaging the patient's heart, as well as to treat bradycardia. Claims 7 and 37-38 also fail to recite a specific dosage of botulinum toxin to be administered. Although claims 15-17 recite dosage ranges of botulinum toxin, these ranges are quite broad as compared to the dosages recited in Masato et al. (pg 260, ¶ 2, ¶ 5). There is no guidance in the instant

specification or the claims as to a specific dosage or duration of treatment of any botulinum toxin to the SA node or AV node of the heart.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Bridget E. Bunner
December 1, 2003

Conferees
Gary Kunz
Yvonne Eyler

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

STEPHEN DONOVAN
LEGAL DEPTALLERGAN INC TOWER TWO 7TH FLR
2525 DUPONT DRIVE
IRVINE, CA 92623-9534